**CRASH trial collaborators. Effect of intravenous corticosteroids on death within 14 days in 10,008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet 2004;364:1321-28.**

Design: Randomized clinical trial

Population/sample size/setting:

- 10,008 patients (mean age 37) in 239 hospitals in 49 countries with head injury seen within 8 hours of injury with a GCS score of 14 or less
- Eligibility was limited only by the treating doctor's uncertainty about the need for corticosteroids
    - If the doctor was substantially uncertain about whether to treat with steroids, the patient could be randomized
    - If the doctor noted a clear indication for or against the use of steroids, the patient was not randomized

Main outcome measures:

- Randomization occurred in one of two ways, depending on the reliability of telephone access to the trial center in Oxford, UK
- All participating hospitals in Europe and Asia were furnished before the trial with numbered treatment packs containing either methylprednisolone or placebo
- If there was good telephone access, a 3 minute call recorded baseline data in the central computer, which generated a treatment allocation number; the allocated pack was opened and administered to the patient (n=2141)
- If there was not good telephone access, an encrypted e-mail was sent to the central computer, and the pack with the allocated number was sent to the participating hospital for opening and administration (n=7867)
- The loading dose of methylprednisolone was 2 g over 1 hr in a 100 ml infusion of normal saline; the maintenance dose was 0.4 g per hour for 48 hours at an infusion rate of 20 ml/hr
- Death from any cause within 14 days of injury was obtained electronically and entered in the trial database, together with data on events in the first 14 days: hematemesis, melena, wound infection, pneumonia, any neurosurgical intervention, and the presence or absence of extracranial injury
- Prespecified subgroup analyses were done on two main baseline characteristics of the patients: time from injury to randomization (<= 1 hr, 1 to 3 hr, or 3 to 8 hr) and severity of injury on the GCS (severe, moderate, mild)
- 5007 patients were allocated methylprednisolone and 5001 were allocated placebo
- Mortality data within 14 days was obtained for 9964 patients; in the methylprednisolone group, the mortality was 21%, while the mortality in the placebo group was 18%
- The relative risk of death with methylprednisolone was 1.18 (95% confidence interval was 1.09-1.27) compared with placebo

- The risk of death was not affected by baseline GCS severity or time elapsed from injury to randomization, nor did it depend on CT findings at baseline (hematoma, midline shift, etc) or on the presence or absence of extracranial injury

Authors' conclusions:

- The trial results reliably refute any reduction in mortality within 2 weeks of head injury with methylprednisolone
- Although the participating hospitals may have varied with respect to concurrent interventions, similar numbers of patients were allocated methylprednisolone and placebo at each hospital
- One limitation may be that the cause of death was not recorded; however, there was no evidence of a large rise in risk of GI or infectious complications to explain the mortality increase
- Corticosteroids should not be used routinely to treat head injury

Comments:

- Overall the conduct of the study protects against significant sources of bias, and the large number of patients provides sufficient power to support the main conclusion that methylprednisolone does not reduce mortality in head injury
- It is not reported whether the mortality relative risk was the same in the different participating centers (or even on different continents); it would be of some interest to have data on the relative risk in Level I Trauma Centers versus community hospitals
- The lack of information on cause of death is not a limitation for the conclusion of the study; all-cause mortality is the most important outcome, regardless of cause

Assessment: High quality for good evidence that early administration of methylprednisolone does not reduce mortality and may increase the risk of death for head injury